10.1161/CIRCULATIONAHA.120.051675

Effect of Dapagliflozin on Clinical Outcomes in Patients with Chronic Kidney Disease, With and Without Cardiovascular Disease

Running Title: *McMurray et al.; Dapagliflozin and Outcomes in Chronic Kidney Disease*

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This manuscript was sent to Dr. Todd M. Brown, Guest Editor, for review by expert referees, editorial decision, and final disposition.

This work was presented as an abstract at the American Heart Association Scientific Sessions, November 13 to November 17, 2020.

Abstract

Background: Dapagliflozin reduces the risk of end-stage renal disease in patients with chronic kidney disease. We examined the relative risk of cardiovascular and kidney events in these patients and the effect of dapagliflozin on either type of event, taking account of history of cardiovascular disease.

Methods: In the DAPA-CKD trial (Dapagliflozin And Prevention of Adverse Outcomes in Chronic Kidney Disease), 4304 participants with chronic kidney disease were randomized to dapagliflozin 10 mg once daily or placebo. The primary endpoint was a composite of sustained decline in estimated GFR ≥50%, end-stage kidney disease, or kidney or cardiovascular death. The secondary endpoints were a kidney composite outcome (primary endpoint, minus cardiovascular death), the composite of hospitalization for heart failure or cardiovascular death and all-cause death. In a prespecified subgroup analysis, we divided patients into primary and secondary prevention subgroups according to history of cardiovascular disease.

Results: Secondary prevention patients (n=1610; 37.4%) were older, more often male, had a higher blood pressure and body-mass index, and were more likely to have diabetes. Mean estimated glomerular filtration rate and median urinary albumin-to-creatinine ratio was similar in the primary and secondary prevention groups. The rates of adverse cardiovascular outcomes were higher in the secondary prevention group, but kidney failure occurred at the same rate in the primary and secondary prevention groups. Dapagliflozin reduced the risk of the primary composite outcome to a similar extent in both the primary (HR, 0.61 [95% CI, 0.48–0.78]) and secondary (0.61, 0.47–0.79) prevention groups (P-interaction=0.90). This was also true for the composite of heart failure hospitalization or cardiovascular death (0.67, 0.40–1.13 versus 0.70, 0.52–0.94, respectively, P-interaction=0.88), and all-cause (0.63, 0.41–0.98 versus 0.70, 0.51–0.95, respectively, P-interaction=0.71). Rates of adverse events were low overall and did not differ between patients with and without cardiovascular disease.

Conclusions: Dapagliflozin reduced the risk of kidney failure, death from cardiovascular causes or hospitalization for heart failure, and prolonged survival, in people with chronic kidney disease, with or without type 2 diabetes, independently of the presence of concomitant cardiovascular disease

Clinical Trial Registration: URL: https://clinicaltrials.gov Unique Identifier: NCT03036150

Key Words: Dapagliflozin; SGLT2 inhibitor; Chronic kidney disease; cardiovascular disease; Heart failure

Non-standard Abbreviations and Acronyms

CREDENCE - The Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation trial
CRT - cardiac resynchronization therapy
CV – cardiovascular
DAPA-CKD - Dapagliflozin And Prevention of Adverse Outcomes in Chronic Kidney Disease trial
DAPA-HF - Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure trial
SGLT2 - sodium glucose cotransporter 2
T2D - type 2 diabetes
UACR - Urinary albumin-to-creatinine ratio

Clinical Perspective

What is new?

- The primary and secondary preventive effects of SGLT2 inhibitors on cardiovascular outcomes have not been studied in patients with CKD, with and without T2D.
- Dapagliflozin reduced the risk of the primary composite outcome to a similar extent in the primary and secondary prevention groups. This was also true for the composite of heart failure hospitalization or cardiovascular death (and all-cause mortality. .

What are the clinical implications?

- The combined cardiorenal benefits of SGLT2 inhibitors in patients with chronic kidney disease, with and without T2D, are substantial, whether there is a history of cardiovascular disease or not.

Introduction

A series of large randomized controlled trials have shown sodium glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of cardiovascular events in people with type 2 diabetes mellitus.[1-3] Overall, these trials showed consistent, sizeable, reductions in heart failure hospitalization with SGLT2 inhibitors whereas the benefit on atherothrombotic events such as myocardial infarction and stroke was modest and, in metanalyses, appeared confined to patients with known cardiovascular disease.[4,5] In contradistinction, reduction in heart failure hospitalization was seen in people with and without a history of cardiovascular disease.[1-5] The Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation trial (CREDENCE) extended these findings to patients with type 2 diabetes mellitus and chronic kidney disease, who are at exceptionally high risk of adverse cardiovascular outcomes.[6] In CREDENCE, canagliflozin reduced the risk of the primary composite renal endpoint, as well as the key secondary composite outcomes of cardiovascular death or hospitalization for heart failure and cardiovascular death, myocardial infarction or stroke. These benefits of canagliflozin were consistent in participants with and without a history of cardiovascular disease.[7]

However, diabetes is not the only cause of chronic kidney disease and people with chronic kidney disease due to other causes are also at heightened risk of adverse cardiovascular outcomes, even if they do not have preexisting cardiovascular disease.[8-11] Consequently, treatments that are both effective and safe are needed for the primary and secondary prevention of cardiovascular events in the broad spectrum of patients with chronic kidney disease, regardless of concomitant type 2 diabetes.

Here we report the effects of dapagliflozin on the prespecified kidney and cardiovascular outcomes in patients with chronic kidney disease with and without type 2 diabetes, according to history of cardiovascular disease, in the Dapagliflozin And Prevention of Adverse Outcomes in Chronic Kidney Disease trial (DAPA-CKD).[12-14]

Methods

DAPA-CKD was a randomized, double-blind, placebo-controlled, multicenter trial and the design, baseline findings and primary results are published.[12-14] The study was registered at clinicaltrials.gov (NCT03036150). All participants provided written informed consent and the trial was approved by an ethics committee at each site. Data supporting the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy (https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure).

Patients

Adults with or without type 2 diabetes, an estimated glomerular filtration rate (eGFR) between 25 and 75 ml/min/1.73 m^2, and a urinary albumin-to-creatinine ratio (UACR) between 200 and 5000 mg/g were eligible. Unless intolerant, participants were required to be prescribed an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) in a stable dose for at least 4 weeks before screening. Key exclusion criteria included: type 1 diabetes, polycystic kidney disease, lupus nephritis, anti-neutrophil cytoplasmic antibody-associated vasculitis, and patients receiving immunotherapy for primary or secondary renal disease within 6 months prior to enrolment. The full inclusion and exclusion criteria are described elsewhere.[12]

Treatment and follow-up

Participants were randomized to dapagliflozin 10 mg once daily or placebo, with stratification by diagnosis of type 2 diabetes and UACR (≤1000 mg/g or >1000 mg/g). Randomization was monitored to ensure at least 30% of the patients had type 2 diabetes and at least 30% did not. After randomization, study visits were planned at 2 weeks, 2, 4, and 8 months and at 4-month intervals thereafter. A recommendation by the Independent Data Monitoring Committee March 26, 2020 that the trial be discontinued early for overwhelming efficacy was accepted and the trial closed out, with April 3, 2020 chosen as the cutoff date for all efficacy analyses. The resultant median follow-up was 2.4 years (interquartile range 2.0 to 2.7 years).

Definition of baseline cardiovascular disease

We prespecified that we would examine the effect of dapagliflozin in patients according to history of cardiovascular disease. For this analysis we divided participants into those with and without baseline cardiovascular disease. Cardiovascular disease was defined as any of the following: coronary heart disease (angina pectoris, myocardial infarction, coronary artery stenosis, percutaneous coronary intervention, coronary artery bypass surgery); cerebrovascular disease (ischemic stroke, hemorrhagic stroke, carotid artery stenosis, transient ischemic attack); peripheral artery disease (peripheral arterial occlusive disease, aneurysm of the abdominal aorta, non-coronary revascularization, vascular stent); heart failure (heart failure, cardiac resynchronization therapy [CRT]); valvular heart disease; atrial fibrillation or atrial flutter; ventricular arrhythmia; pulmonary embolism, and cardiac devices other than CRT (cardiac pacemaker, implantable cardioverter defibrillator [ICD]).

Prespecified and *post hoc* trial outcomes

The primary composite outcome was the time to the first occurrence of any of the following ≥50% decline in eGFR (confirmed by a second serum creatinine measurement after at least 28 days), onset of end-stage kidney disease (defined as maintenance dialysis for more than 28 days, kidney transplantation, or eGFR <15 ml/min/1.73 m^2 confirmed by a second measurement after at least 28 days), or death from kidney or cardiovascular cause.

Prespecified secondary outcomes were, in hierarchal order: 1) a kidney composite outcome identical to the primary endpoint, with the exception of death from cardiovascular causes; 2) a cardiovascular composite outcome consisting of hospitalization for heart failure or death from cardiovascular causes; and 3) death from any cause. A blinded independent committee adjudicated all components of the primary and secondary outcomes except for changes in eGFR which were calculated from central laboratory measurements. Deaths with an undetermined cause were assumed to be cardiovascular.

In this study we also examined two prespecified exploratory outcomes: 1) a cardiovascular composite outcome of time to first occurrence of myocardial infarction, stroke or death from cardiovascular causes and 2) time-to-first heart failure hospitalization.

Lastly, we examined two *post hoc* composite outcomes (analyzed as time-to-first event): 1) myocardial infarction, stroke, heart failure hospitalization or death from cardiovascular causes (to examine all major adverse cardiovascular events) and 2) myocardial infarction, stroke, heart failure hospitalization, end-stage kidney disease or death from any cause (to examine all the major non-fatal and fatal adverse outcomes patients with chronic kidney disease face).
As in prior dapagliflozin outcome trials, we collected only selected adverse event data, including serious adverse events, adverse events resulting in the discontinuation of trial treatment, and

"adverse events of interest" which included symptoms of volume depletion, renal events, major hypoglycemia, bone fractures, amputations, and diabetic ketoacidosis (potential diabetic ketoacidosis events were adjudicated by an independent committee).[3,12]

Statistical Analysis

The efficacy analyses included all randomized participants and were conducted according to the intention-to-treat principle. Cox proportional hazard regression models including the stratification variables and adjusted for baseline eGFR were used to estimate the hazard ratio (HR) and 95% confidence intervals (CI) for dapagliflozin compared to placebo for the primary and secondary study outcomes. HRs (95% CIs) for the effect of dapagliflozin 10 mg, compared with placebo, were obtained separately for the cardiovascular disease and no cardiovascular disease subgroups using Cox proportional hazards models with a factor for treatment group, stratified by randomization stratification factors (type 2 diabetes, UACR), and adjusting for baseline eGFR. Interaction p-values were based on likelihood ratio tests comparing full factorial models against reduced models with main effects only (again stratified by randomization stratification factors and adjusted for baseline eGFR). Treatment effects are not presented for variables with less than 15 events in total (both arms combined). Time-to-event data are illustrated using Kaplan–Meier curves.

Safety data are reported by treatment group in all patients who received at least one dose of randomized treatment.

All analyses were performed with R (Version 4.02).

Results

Of the 4304 patients randomized, 1610 (37.4%) had a diagnosis of cardiovascular disease at baseline ("secondary prevention" patients) and 2694 (62.6%) participants did not have a history of cardiovascular disease ("primary prevention" patients).

Baseline characteristics

The baseline characteristics of patients with and without cardiovascular disease are shown in Table 1. Patients with cardiovascular disease were older (66.3 versus 59.2 years), more often male (70.5% versus 64.7%) and smokers (52.6 versus 43.2% current or prior smokers), had a higher mean systolic blood pressure (139.2 versus 135.8 mmHg) and higher body mass index (30.6 versus 28.9 Kg/m^2) and were more likely to have diabetes (79.6 versus 60.3%) than those without a history of cardiovascular disease. Mean eGFR and median UACR were similar in patients with and without cardiovascular disease.

Among patients in the secondary prevention group, 56% had coronary artery disease, 29% cerebrovascular disease, 26% peripheral artery disease, 29% heart failure and 14% atrial fibrillation/flutter. Almost all patients in each of the primary and secondary prevention groups had hypertension. Use of cardiovascular pharmacological therapy, overall, was greater in secondary prevention patients compared with primary prevention patients (Table 1).

Primary outcome and kidney outcomes according to baseline history of cardiovascular disease

Comparing all trial participants, irrespective of randomized treatment assignment, the primary composite outcome of sustained decline in eGFR of at least 50%, end-stage kidney disease or death from cardiovascular disease or kidney failure, occurred at a rate of 7.0 (95%CI 6.2-8.0) per 100 person-years in the patients with a history of cardiovascular disease, compared with a rate of

5.4 (95%CI 4.8-6.0) per 100 person-years in patients without a history of cardiovascular disease, hazard ratio (HR) 1.24; 95%CI 1.04-1.48; P=0.02). The higher rate of the primary outcome in the secondary prevention patients was due to a higher rate of cardiovascular death in these participants: 2.9 (95%CI 2.3-3.5) per 100 person-years compared with 0.8 (95%CI 0.6-1.0) per 100 person years in the primary prevention patients. The rate of the key secondary, kidney-specific, composite of sustained decline in eGFR of at least 50%, end-stage kidney disease or death from kidney cause was similar in these two patient groups: 4.3 (95%CI 3.6-5.0) per 100 person-years in the patients with a history of cardiovascular disease, compared with a rate of 4.7 (95%CI 4.2-5.4) per 100 person-years in the primary prevention group (HR 0.87; 95%CI 0.70-1.07; P=0.18).

Cardiovascular outcomes and all-cause mortality according to baseline history of cardiovascular disease

The key secondary composite outcome of cardiovascular death or hospitalization for heart failure occurred at a more than 4-fold higher rate in secondary prevention patients compared with primary prevention patients: 5.2 (95%CI 4.4-6.0) per 100 person-years in the secondary prevention group compared with 1.0 (95%CI 0.83-1.3) per 100 person-years in the primary prevention group (HR 4.52; 95%CI 3.36-6.07; P<0.001). Likewise, the rate of the prespecified composite of cardiovascular death, myocardial infarction or stroke occurred at a higher rate in patients with a history of cardiovascular disease compared to those without: 5.4 (95%CI 4.6-6.2) per 100 person-years in the secondary prevention group compared with 1.6 (95%CI 1.3-2.0) per 100 person-years in the primary prevention group (HR 3.10; 95%CI 2.41-4.00; P<0.001). Death from any cause also occurred more frequently in patients with a history of cardiovascular disease, compared to those without, although the difference between groups was not as large as

for the aforementioned endpoints: 4.6 (95%CI 3.9-5.3) per 100 person-years in the secondary prevention group compared with 1.5 (95%CI 1.2-1.8) per 100 person-years in the primary prevention group (HR 2.90; 95%CI 2.22-3.78; P<0.001).

Effect of dapagliflozin on prespecified clinical outcomes according to baseline history of cardiovascular disease

Among patients with cardiovascular disease, the primary composite outcome occurred in 91 (11.2%) participants in the dapagliflozin group and 137 (17.2%) participants in the placebo group (HR 0.61; 95%CI, 0.47-0.79); the corresponding numbers were 106 (7.9%) and 175 (12.9%) in participants without cardiovascular disease (HR 0.61; 0.48-0.78); P-interaction = 0.90 (Table 2 and Figures 1 and 2). In both the primary and secondary prevention patients, the event rates favored dapagliflozin for all components of the primary outcome, as well as for the key, kidney-specific, secondary endpoint, although the reduction in cardiovascular death was not statistically significant (Table 2).

Among patients with cardiovascular disease, the key secondary composite outcome of cardiovascular death or hospitalization for heart failure occurred in 76 (9.3%) participants in the dapagliflozin group and 102 (12.8%) participants in the placebo group (HR 0.70; 0.52-0.94); the corresponding numbers were 24 (1.8%) and 36 (2.7%) in participants without cardiovascular disease (HR 0.67; 0.40-1.13); P-interaction = 0.88 (Table 2 and Figures 1 and 2). The reduction in risk was driven by heart failure hospitalization which occurred in 33 (4.1%) participants in the dapagliflozin group and 58 (7.3%) participants in the placebo group with cardiovascular disease (HR 0.54; 0.35-0.82); the corresponding numbers in participants without cardiovascular disease were 4 (0.3%) and 13 (1.0%) (HR 0.31; 0.10-0.94); P-interaction = 0.35.

Dapagliflozin did not decrease the risk of the prespecified composite of cardiovascular death, myocardial infarction or stroke significantly in either the secondary or primary prevention group (Table 2).

Effect of dapagliflozin on post hoc cardiovascular and cardiorenal composite outcomes according to baseline history of cardiovascular disease

Among patients with cardiovascular disease, the expanded cardiovascular composite outcome (death from cardiovascular causes, myocardial infarction, stroke or hospitalization for heart failure) occurred in in 114 (14.0%) participants in the dapagliflozin group and 135 (16.9%) participants in the placebo group (HR 0.80; 0.62-1.03); the corresponding numbers were 44 (3.3%) and 60 (4.4%) in participants without cardiovascular disease (HR 0.73; 0.50-1.08); P-interaction = 0.72 (Table 2).

Among patients with cardiovascular disease, the cardiorenal composite outcome (death from any cause, myocardial infarction, stroke, heart failure hospitalization, or end-stage kidney disease) occurred in 156 (19.2%) participants in the dapagliflozin group and 199 (25.0%) participants in the placebo group (HR 0.72; 0.58-0.89); the corresponding numbers were 118 (8.8%) and 177 (13.1%) in participants without cardiovascular disease (HR 0.68; 0.54-0.85); P-interaction = 0.77 (Table 2). The number of patients needed to treat (NNT) over the duration of the trial to prevent one experiencing this broad composite endpoint was 21 (95% CI 15, 38) in the overall population; in primary prevention patients the NNT was 24 (15, 53) and in secondary prevention patients it was 17 (10, 58).

Safety outcomes and adverse events

The rates of all prespecified adverse events of interest were low overall and generally similar in the primary and secondary prevention subgroups, excepting amputation, which occurred more

often in participants with a history of cardiovascular disease (Table 3). Adverse event rates, including for amputation, were similar overall in patients assigned to dapagliflozin and placebo, irrespective of history of cardiovascular disease (Table 3).

Discussion

In DAPA-CKD, among participants with chronic kidney disease, with and without type 2 diabetes, over a third had a history of cardiovascular disease.[12-14] While the cardiovascular risk of participants differed markedly in relation to baseline cardiovascular disease status, renal risk did not. Dapagliflozin was similarly efficacious in reducing the risk of adverse kidney outcomes, the composite outcome of cardiovascular death or hospitalization for heart failure, and death from any cause, irrespective of history of cardiovascular disease at baseline.

The dichotomy in rates of the prespecified renal and cardiovascular endpoints in the primary and secondary prevention patient subgroups was striking. While the rate of the kidney-specific endpoint was the same in participants regardless of history of cardiovascular disease, the rate of the composite of cardiovascular death or hospitalization for heart failure was 5-times higher in those with known cardiovascular disease (secondary prevention group) compared to participants with no history of cardiovascular disease (primary prevention group). Likewise, the rate of the prespecified exploratory composite of cardiovascular death, myocardial infarction or stroke was similarly elevated in secondary prevention, compared with primary prevention, participants. As a result, the rate of cardiovascular events, and death, was considerably higher than the rate of adverse kidney outcomes in patients with a history of cardiovascular disease, whereas the reverse was true in the primary prevention participants, although the differential risk was not as marked.

Our finding of a heightened risk of cardiovascular events in the secondary prevention patients, compared with primary prevention patients, is not unexpected and consistent with the findings of CREDENCE.[7] However, the much greater differential risk between the primary and secondary prevention populations in DAPA-CKD compared with CREDENCE is more notable, likely reflecting differences in trial design, participants and definitions of cardiovascular disease. The secondary prevention patients in CREDENCE had around a 2-fold higher rate of adverse cardiovascular outcomes, compared with primary prevention patients, whereas this risk difference was 3- to 5-fold in DAPA-CKD. As a result, while the rates of the prespecified cardiovascular outcomes were similar in secondary prevention patients in CREDECE and DAPA-CKD, the rates of these outcomes in primary prevention patients were much lower in DAPA-CKD than in CREDENCE. [6,7] One probable explanation for this difference was the requirement for all participants in CREDENCE to have type 2 diabetes whereas only 60% of patients in the DAPA-CKD primary prevention subgroup had diabetes, a condition that substantially augments cardiovascular risk.[6,7] Baseline cardiovascular disease was also defined differently in the two trials, with heart failure not included as cardiovascular disease in CREDENCE. [6,7]

More importantly, dapagliflozin reduced the risk of adverse kidney outcomes irrespective of baseline cardiovascular disease status and this was also true for the main secondary cardiovascular composite outcome, which was the composite of heart failure hospitalization or cardiovascular death, although there were relatively few of the latter events in the primary prevention group. However, dapagliflozin did not reduce the prespecified exploratory composite of cardiovascular death, myocardial infarction or stroke overall, or in the secondary prevention subgroup.

Focusing on the cardiovascular outcomes, SGLT2 inhibitors clearly reduce heart failure hospitalization and the treatment effect size in DAPA-CKD was particularly large with an approximate halving of the risk of this outcome, with a consistent proportional risk reduction in primary and secondary prevention patients. This finding is important in two respects. First, it cements the evidence that the benefit of SGLT2 inhibitors on heart failure is independent of background atherosclerotic disease and is not mediated through prevention of atherosclerotic events.[1-7] Second, it extends the evidence that SGLT2 inhibitors prevent a common, disabling and deadly cardiovascular complication in patients with chronic kidney disease overall, that is heart failure, to people without diabetes as well as without known cardiovascular disease (although the risk of heart failure was relatively low in the latter patients during the relatively short- to medium-term follow-up in DAPA-CKD).[10,15,16]

The composite of cardiovascular death, myocardial infarction or stroke was not reduced in DAPA-CKD, unlike CREDENCE.[6,7] The likely explanation for this difference is lack of statistical power as approximately twice as many patients in CREDENCE experienced at least one of these events, compared with DAPA-CKD, reflecting the higher proportion of patients with baseline cardiovascular disease (50.4% versus 37.4%) and diabetes (100% versus 60.3%) in CREDENCE.

Another difference between the two trials was the reduction in death from any cause in DAPA-CKD, which was not observed in CREDENCE. This effect in DAPA-CKD was consistent in patients with and without a history of cardiovascular disease, extending another critically important clinical benefit to people with chronic kidney disease without diabetes and to these patients without cardiovascular disease as well. The mortality benefit also supports the

findings of DAPA-HF (Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure trial).[17]

Finally, although not prespecified, we examined a "cardiorenal" composite outcome reflecting the overall disease burden faced by patients with chronic kidney disease and the full spectrum of events, each of which an ideal treatment would reduce (death from any cause, myocardial infarction, stroke, heart failure hospitalization, or end-stage kidney disease). Dapagliflozin led to an approximately 30% relative risk reduction in this outcome, and this effect was consistent in the primary and secondary prevention subgroups. The absolute risk reductions of 4-6% were also substantial, irrespective of history of cardiovascular disease. The resultant number needed to treat (NNT) was ranged from 24 in the primary prevention subgroup to 24 in the secondary prevention participants to prevent one patient experiencing a major fatal or nonfatal adverse renal or cardiovascular outcome, over a median of 2.3 years.

As with any study of this type, there are certain limitations. Our patients were enrolled in a clinical trial and, therefore, were selected by virtue of the inclusion and exclusion criteria and other factors that influence participation in trials. Some of the analyses were not prespecified. Certain events were infrequent (e.g. death from renal causes) and the effect of treatment on these could not be assessed reliably.

In summary, dapagliflozin reduced the risk of kidney failure, death from cardiovascular causes or hospitalization for heart failure, and prolonged survival, in people with chronic kidney disease, independently of the presence of concomitant cardiovascular disease.

Sources of Funding

The DAPA-CKD trial was funded by AstraZeneca. Professor John J V McMurray is supported by a British Heart Foundation Centre of Research Excellence Grant RE/18/6/34217

Disclosures

JMcM Payments to my employer, Glasgow University, for my work on clinical trials, consulting and other activities: Alnylam, Amgen, AstraZeneca, Bayer, BMS, Cardurion, Cytokinetics, GSK, Novartis, Pfizer, Theracos. Personal lecture fees: the Corpus, Abbott, Hickma, Sun Pharmaceuticals, Medsca.

DCW has received honoraria and/or consultancy fees from Amgen, AstraZeneca, Boehringer Ingelhiem, Bayer, GlaxoSmithKline, Janssen, Napp, Mundipharma, Medscape, Merck Sharp and Dohme, Pharmacosmos, Reata, Takeda, and Vifor Fresenius.

NJ has nothing to declare.

GMC has received fees from AstraZeneca for the DAPA-CKD trial steering committee, research grants from NIDDK, and Amgen; he is on the board of directors for Satellite Healthcare, has received fees for advisory boards for Baxter, Cricket, DiaMedica, and Reata; and holds stock options for Ardelyx, CloudCath, Durect, DxNow, and Outset; has received fees from Akebia, Sanifit and Vertex for Trial steering committees; and has received fees for DSMB service from Angion, Bayer and ReCor.

TG has received grants for statistical consulting from AstraZeneca, CSL and Boehringer-Ingelheim; has received personal fees from Janssen Pharmaceuticals, DURECT Corporation and Pfizer for statistical consulting.

CH has received grants and personal fees from Astra Zeneca,; grants and personal fees from Boehringer Ingelheim, grants and personal fees from Pfizer, personal fees from Coala Life, grants and personal fees from Bayer.

FFH has received honoraria from AbbVie and AstraZeneca.

JFEM reports receipt of speaker honoraria from AstraZeneca, Boehringer Ingelheim, Bayer, Fresenius, Medice, Novo Nordisk, Relypsa, Roche; research support from European Union, Canadian Institutes Health Research, Boehringer Ingelheim, Celgene, Idorsia, Novo Nordisk, Roche, Sandoz; and consultation fees from AstraZeneca, Bayer, Celgene, Novo Nordisk, Vifor Pharma

PR has received honoraria to Steno Diabetes Center Copenhagen for consultancy from AstraZeneca, Astellas, Bayer, Boehringer Ingelheim, Gilead, Novo Nordisk, Merck, Mundipharma, Sanofi, Vifor, and research support from Astra Zeneca and Novo Nordisk

RC-R has received honoraria from AbbVie, AstraZeneca, GlaxoSmithKline, Medtronic, and Boehringer Ingelheim, and has lectured for Amgen, Janssen, Takeda, AstraZeneca, and Boehringer Ingelheim and has received research support from GlaxoSmithKline, Novo Nordisk and AstraZeneca.

RDT is a consultant for AstraZeneca, Amgen, Bayer, Boehringer-Ingelheim, Medscape, Otsuka, Reata and Relypsa.

BVS, CDS, and AML are employees and stockholders of AstraZeneca.

HJLH is consultant for AbbVie, AstraZeneca, Bayer, Boehringer Ingelheim, Chinook, CSL Pharma, Gilead, Janssen, Merck, Mundi Pharma, Mitsubishi Tanabe, Novo Nordisk, and Retrophin. He received research support from Abbvie, AstraZeneca, Boehringer Ingelheim and Janssen.

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Table 1. Characteristics of the patients at baseline according to baseline cardiovascular disease and randomized treatment assignment.

	Baseline cardiovascular disease (n= 1610)		**No baseline cardiovascular disease (n=2694)**	
	Dapagliflozin	**Placebo**	**Dapagliflozin**	**Placebo**
	N= 813	**N= 797**	**N= 1339**	**N= 1355**
Age – years	66.5 (9.7)	66.2 (9.3)	59 (12.5)	59.4 (12.9)
Male sex - no (%)	587 (72.2)	548 (68.8)	856 (63.9)	888 (65.5)
Race – no. (%)				
White	539 (66.3)	523 (65.6)	585 (43.7)	643 (47.5)
Black or African American	37 (4.6)	43 (5.4)	67 (5)	44 (3.2)
Asian	180 (22.1)	173 (21.7)	569 (42.5)	545 (40.2)
Other	57 (7.0)	58 (7.3)	118 (8.8)	123 (9.1)
Region – no. (%)				
Europe	307 (37.8)	288 (36.1)	303 (22.6)	335 (24.7)
Asia/Pacific	165 (20.3)	157 (19.7)	527 (39.4)	497 (36.7)
South America	167 (20.5)	173 (21.7)	282 (21.1)	290 (21.4)
North America	174 (21.4)	179 (22.5)	227 (17.0)	233 (17.2)
Heart rate – beats/min = pulse	71.6 (11.4)	70.7 (11.3)	73.7 (11.4)	74.1 (11.6)
Systolic Blood Pressure – mmHg	138.8 (17.6	139.7 (17.6)	135.5 (17.3)	136.1 (17.0)
HbA1c – %	7.4 (1.7)	7.4 (1.7)	6.9 (1.7)	6.8 (1.7)
Hemoglobin – g/dl	130.1 (17.9)	127.9 (18.4)	127.7 (18.2)	127.9 (17.8)
Current smoker – no. (%)	97 (11.9)	117 (14.7)	186 (13.9)	184 (13.6)
Body-mass index – Kg/m^2	30.3 (6.2)	30.9 (6.5)	28.8 (5.9)	28.9 (6.0)
Obese (body-mass index ≥30 Kg/m^2) – no. (%)	415 (51.0)	435 (54.6)	526 (39.3)	541 (39.9)
Medical history – no. (%)				
Any atherosclerotic cardiovascular disease	663 (81.5)	666 (83.6)	-	-
Hypertension	803 (98.8)	788 (98.9)	1262 (94.2)	1268 (93.6)
Heart failure	235 (28.9)	233 (29.2)	-	-
Atrial fibrillation or flutter	115 (14.1)	112 (14.1)	-	-
Angina	201 (24.7)	204 (25.6)	-	-
Myocardial infarction	185 (22.8)	207 (26.0)	-	-
Coronary artery bypass grafting	74 (9.1)	102 (12.8)	-	-
Percutaneous coronary intervention	145 (17.8)	149 (18.7)	-	-

Stroke	144 (17.7)	154 (19.3)	-	-
Transient ischemic attack	41 (5.0)	38 (4.8)	-	-
Peripheral artery disease	154 (18.9)	171 (21.5)	-	-
Amputation	59 (7.3)	50 (6.3)	36 (2.7)	36 (2.7)
Type 2 diabetes	640 (78.7)	641 (80.4)	815 (60.9)	810 (59.8)
Estimated GFR – ml/min/1.73 m^2 of body-surface area	43.3 (12.0)	43.0 (12.6)	43.2 (12.5)	42.9 (12.3)
Estimated GFR category				
≥60 ml/min/1.73 m^2 – no. (%)	94 (11.6)	88 (11.0)	140 (10.5)	132 (9.7)
45-59 ml/min/1.73 m^2 – no. (%)	233 (28.7)	254 (31.9)	413 (30.8)	428 (31.6)
30-44 ml/min/1.73 m^2 – no. (%)	388 (47.7)	322 (40.4)	591 (44.1)	597 (44.1)
<30 ml/min/1.73 m^2 – no. (%)	98 (12.1)	133 (16.7)	195 (14.6)	198 (14.6)
Median UACR (IQR) – mg/g	1012 (446-1956)	944(473-1825)	937 (487-1856)	933 (488-1911)
Device therapy – no (%)				
Implantable cardioverter-defibrillator	8 (1.0)	6 (0.8)	-	-
Cardiac resynchronization therapy	2 (0.2)	4 (0.5)	-	-
Pacemaker	27 (3.3)	28 (3.5)	-	-
Cardiovascular and renal medication – no (%)				
Beta-blocker	495 (60.9)	474 (59.5)	351 (26.2)	360 (26.6)
Diuretic	437 (53.8)	443 (55.6)	491 (36.7)	511 (37.7)
Mineralocorticoid receptor antagonist	65 (8.0)	74 (9.3)	44 (3.3)	46 (3.4)
ACE inhibitor, ARB or other RAS blocker	798 (98.2)	761 (95.5)	1296 (96.8)	1319 (97.3)
Antiplatelet	577 (71.0)	547 (68.6)	375 (28.0)	381 (28.1)
Statin	622 (76.5)	609 (76.4)	773 (57.7)	790 (58.3)
Other lipid lowering therapy	132 (16.2)	115 (14.4)	188 (14.0)	210 (15.5)
Glucose-lowering medication – no (%)				
Biguanide	272 (33.5)	274 (34.4)	362 (27.0)	342 (25.2)
Sulfonylurea	158 (19.4)	156 (19.6)	232 (17.3)	230 (17.0)
DPP-4 inhibitor	133 (16.4)	145 (18.2)	231 (17.3)	233 (17.2)
GLP-1 receptor agonist	30 (3.7)	23 (2.9)	33 (2.5)	36 (2.7)
Insulin	382 (47.0)	367 (46)	432 (32.3)	417 (30.8)

ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; DPP-4: dipeptidyl peptidase; GFR: glomerular filtration rate; GLP-1: glucagon-like peptide 1; HbA1c: hemoglobin A1c (glycated hemoglobin); RAS: renin-angiotensin system; UACR: urinary albumin-to-creatinine ratio

Table 2. Primary, secondary and exploratory end points according to baseline cardiovascular disease status.

	Dapagliflozin (N=2152)		**Placebo (N=2152)**		**Absolute Risk Difference (95% CI)**	**Hazard Ratio (95% CI)**	**Interaction P-value**
	No CV disease (N=1339) CV disease (N=813)		No CV disease (N=1355) CV disease (N=797)				
	No. (%)	Participants with Event/100 Patient-Yr	No. (%)	Participants with Event/100 Patient-Yr			
Primary composite outcome and individual components							
*eGFR decline ≥50%, end-stage kidney disease, or kidney or cardiovascular death**							
No CV disease	106 (7.9)	4.0	175 (12.9)	6.7	-5.0% (-7.3 to -2.7)	0.61 (0.48 to 0.78)	0.90
CV disease	91 (11.2)	5.5	137 (17.2)	8.7	-6.0% (-9.4 to -2.6)	0.61(0.47 to 0.79)	
≥50% estimated GFR decline							
No CV disease	71 (5.3)	2.7	127 (9.4)	4.9	-4.1% (-6.0 to -2.1)	0.57 (0.42 to 0.76)	0.54
CV disease	41 (5.0)	2.5	74 (9.3)	4.7	-4.2% (-6.8 to -1.7)	0.50 (0.34 to 0.73)	
End-stage kidney disease							
No CV disease	72 (5.4)	2.7	106 (7.8)	4.0	-2.4% (-4.3 to -0.6)	0.69 (0.51 to 0.93)	0.50
CV disease	37 (4.6)	2.2	55 (6.9)	3.4	-2.3% (-4.6 to -0.1)	0.59 (0.39 to 0.91)	
Kidney death							
No CV disease	1 (0.1)	0.0	2 (0.1)	0.1	-	-	-
CV disease	1 (0.1)	0.1	4 (0.5)	0.2	-	-	
Cardiovascular death							
No CV disease	20 (1.5)	0.7	24 (1.8)	0.8	-0.3% (-1.2 to 0.7)	0.85 (0.47 to 1.54)	0.80
CV disease	45 (5.5)	2.5	56 (7.0)	3.2	-1.5% (-3.9 to 0.9)	0.77 (0.52 to 1.14)	
Secondary outcomes							
eGFR decline ≥50%, end-stage kidney disease or kidney death							
No CV disease	93 (6.9)	3.6	154 (11.4)	5.9	-4.4% (-6.6 to -2.2)	0.61 (0.47 to 0.79)	0.29
CV disease	49 (6.0)	2.9	89 (11.2)	5.6	-5.1% (-7.9 to -2.4)	0.49 (0.34 to 0.69)	
Cardiovascular death or hospitalization for heart failure							
No CV disease	24 (1.8)	0.8	36 (2.7)	1.3	-0.9% (-2.0 to 0.2)	0.67 (0.40 to 1.13)	0.88
CV disease	76 (9.3)	4.3	102 (12.8)	6.1	-3.4% (-6.5 to -0.4)	0.70 (0.52 to 0.94)	
All-cause death							
No CV disease	33 (2.5)	1.1	53 (3.9)	1.8	-1.4% (-2.8 to -0.1)	0.63 (0.41 to 0.98)	0.71

CV disease	68 (8.4)	3.8	93 (11.7)	5.4	-3.3% (-6.2 to -0.4)	0.70 (0.51 to 0.95)	
Prespecified exploratory cardiovascular outcomes							
Cardiovascular death, myocardial infarction or stroke							
No CV disease	41 (3.1)	1.4	50 (3.7)	1.7	-0.6% (-2.0 to 0.7)	0.83 (0.55 to 1.25)	0.61
CV disease	91 (11.2)	5.2	93 (11.7)	5.5	-0.5% (-3.6 to 2.6)	0.94 (0.71 to 1.26)	
First heart failure hospitalization							
No CV disease	4 (0.3)	0.1	13 (1.0)	0.5	-0.7% (-1.3 to -0.1)	0.31 (0.10 to 0.94)	0.35
CV disease	33 (4.1)	1.9	58 (7.3)	3.5	-3.2% (-5.5 to -1.0)	0.54 (0.35 to 0.82)	
***Post hoc* exploratory cardiovascular/cardiorenal outcomes**							
Cardiovascular death, myocardial infarction, stroke or heart failure hospitalization							
No CV disease	44 (3.3)	1.5	60 (4.4)	2.1	-1.1% (-2.6 to 0.3)	0.73 (0.50 to 1.08)	0.72
CV disease	114 (14.0)	6.6	135 (16.9)	8.3	-2.9% (-6.4 to 0.6)	0.80 (0.62 to 1.03)	
All-cause death, myocardial infarction, stroke, heart failure hospitalization or end-stage kidney disease							
No CV disease	118 (8.8)	4.5	177 (13.1)	6.8	-4.3% (-6.6 to -1.9)	0.68 (0.54 to 0.85)	0.77
CV disease	156 (19.2)	9.6	199 (25.0)	13.1	-5.8% (-9.8 to -1.7)	0.72 (0.58 to 0.89)	

*end-stage kidney disease = eGFR <15 ml/min/1.73 m^2, long-term dialysis or kidney transplantation
CV = cardiovascular; eGFR = estimated glomerular filtration rate

Table 3. Prespecified adverse events (AE) and study drug discontinuation because of adverse events

		Dapagliflozin **No CV disease** **n = 1337** **CV disease** **n = 812** Number (%)	**Placebo** **No CV disease** **n = 1352** **CV disease** **n = 797** Number (%)	**P value for interaction**
Any serious AE	No CV disease CV disease	287 (21.5) 346 (42.6)	371 (27.4) 358 (44.9)	0.09
AE leading to study drug discontinuation	No CV disease CV disease	73 (5.5) 45 (5.5)	70 (5.2) 53 (6.6)	0.36
Amputation	No CV disease CV disease	10 (0.7) 25 (3.1)	15 (1.1) 24 (3.0)	0.40
Fracture	No CV disease CV disease	44 (3.3) 41 (5.0)	44 (3.3) 25 (3.1)	0.15
Renal adverse event	No CV disease CV disease	76 (5.7) 79 (9.7)	99 (7.3) 89 (11.2)	0.61
Volume depletion	No CV disease CV disease	75 (5.6) 52 (6.4)	46 (3.4) 44 (5.5)	0.20
Major hypoglycemia*	No CV disease CV disease	3 (0.2) 11 (1.4)	13 (1.0) 15 (1.9)	0.12

CV = cardiovascular. AE = adverse event

*The following criteria were confirmed by the investigator: symptoms of severe impairment in consciousness or behavior, need of external assistance, intervention to treat hypoglycemia, and prompt recovery from acute symptoms after the intervention.

Definite or probable ketoacidosis occurred in 2 patients without CV disease randomly allocated to placebo; there were no cases of ketoacidosis in the dapagliflozin group.

Figure Legends

Figure 1. The effect of dapagliflozin, compared with placebo, on a) Primary composite outcome; b) composite of hospitalization for heart failure or death from cardiovascular causes and c) death from any cause (prespecified secondary outcomes) and d) the exploratory composite of myocardial infarction, stroke, heart failure hospitalization, end-stage kidney disease or death from any cause.

The primary composite outcome was time to the first occurrence of any of the following ≥50% decline in eGFR (confirmed by a second serum creatinine measurement after at least 28 days), onset of end-stage kidney disease (defined as maintenance dialysis for more than 28 days, kidney transplantation, or eGFR <15 ml/min/1.73 m2 confirmed by a second measurement after at least 28 days), or death from kidney or cardiovascular cause, according to history of cardiovascular disease at baseline.

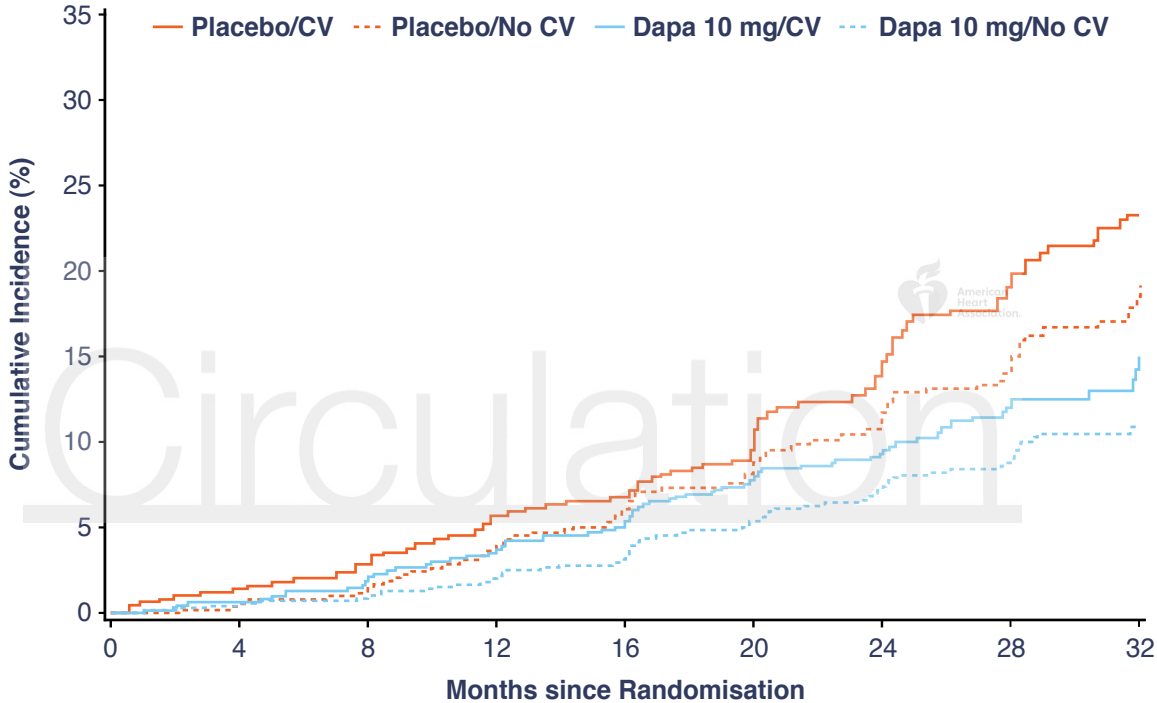
One prespecified secondary outcome is not shown and was a kidney composite outcome identical to the primary endpoint, excepting death from cardiovascular causes.

CV = cardiovascular

Figure 2. Prespecified and post hoc outcomes overall, and according to history of cardiovascular disease at baseline

CV = cardiovascular eGFR = eGFR = estimated glomerular filtration rate ESKD = end-stage kidney disease

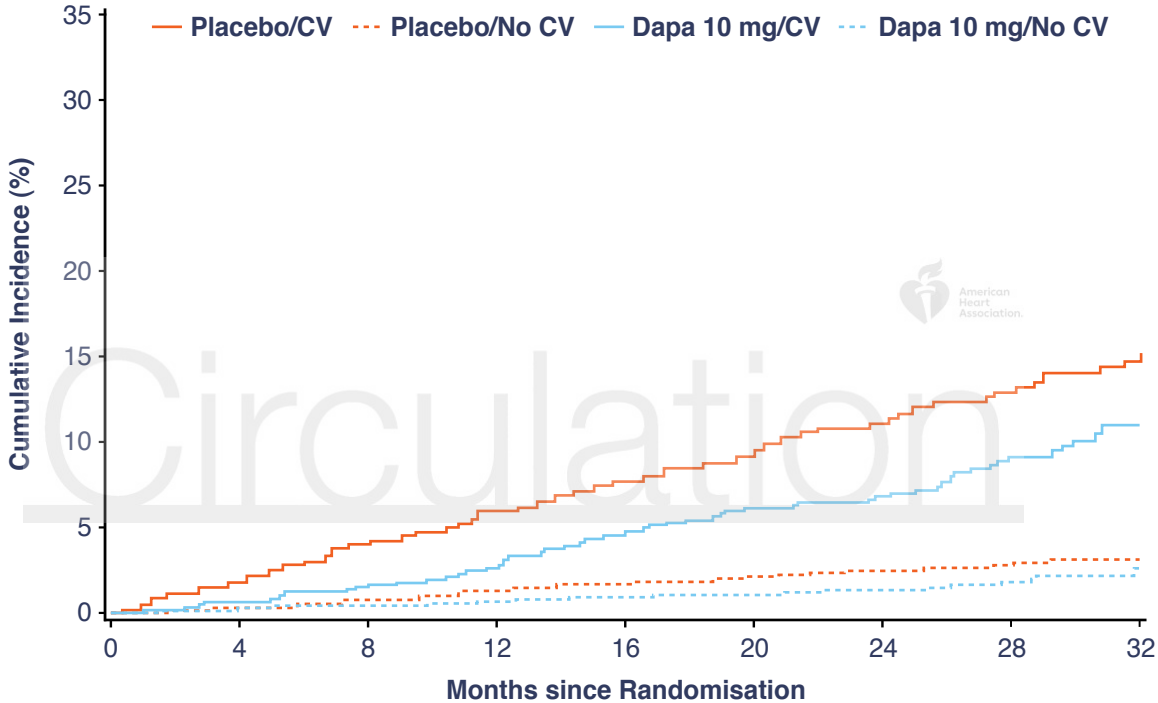
Primary endpoint by CV history



No at Risk

Dapa 10mg/CV	813	780	760	736	710	650	510	326	124
Dapa 10mg/No CV	1339	1221	1195	1162	1131	1051	778	505	185
Placebo/CV	797	757	734	703	677	626	470	289	94
Placebo/No CV	1355	1236	1202	1155	1114	1038	762	485	176

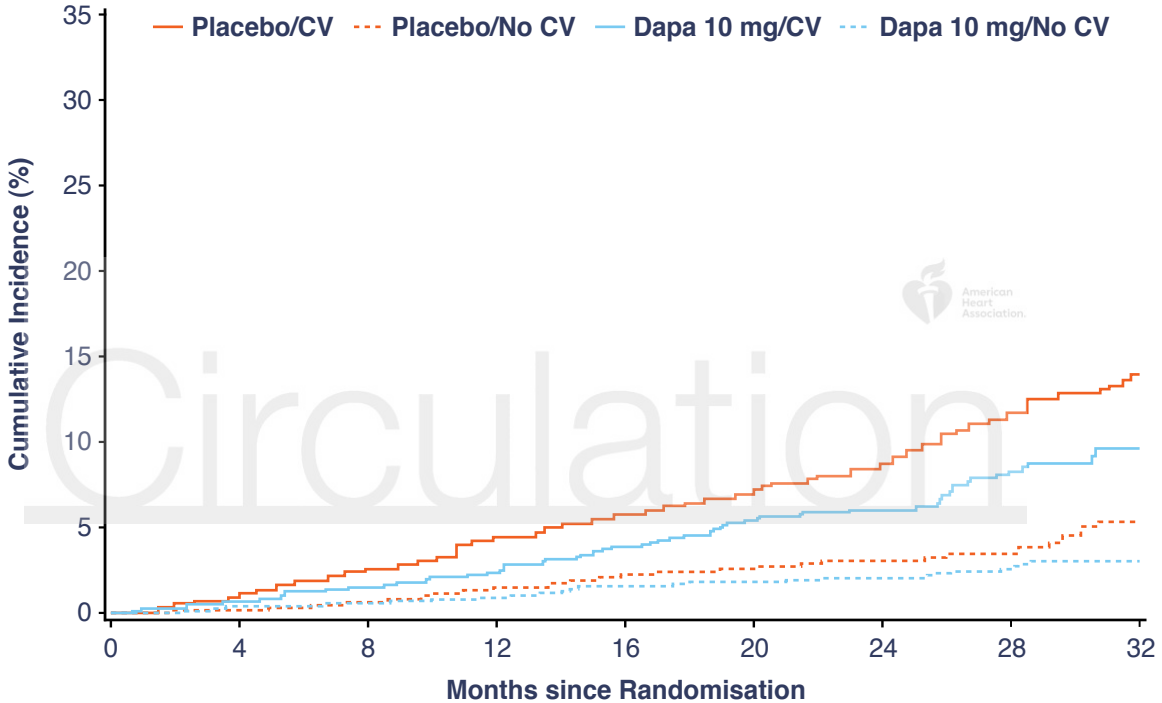
Composite of HF hospitalization or CV death by CV history



No. at Risk

Dapa 10mg/CV	813	787	779	767	747	712	581	384	150
Dapa 10mg/No CV	1339	1248	1242	1236	1228	1183	921	619	234
Placebo/CV	797	761	740	721	703	671	531	366	124
Placebo/No CV	1355	1262	1249	1236	1224	1182	920	610	236

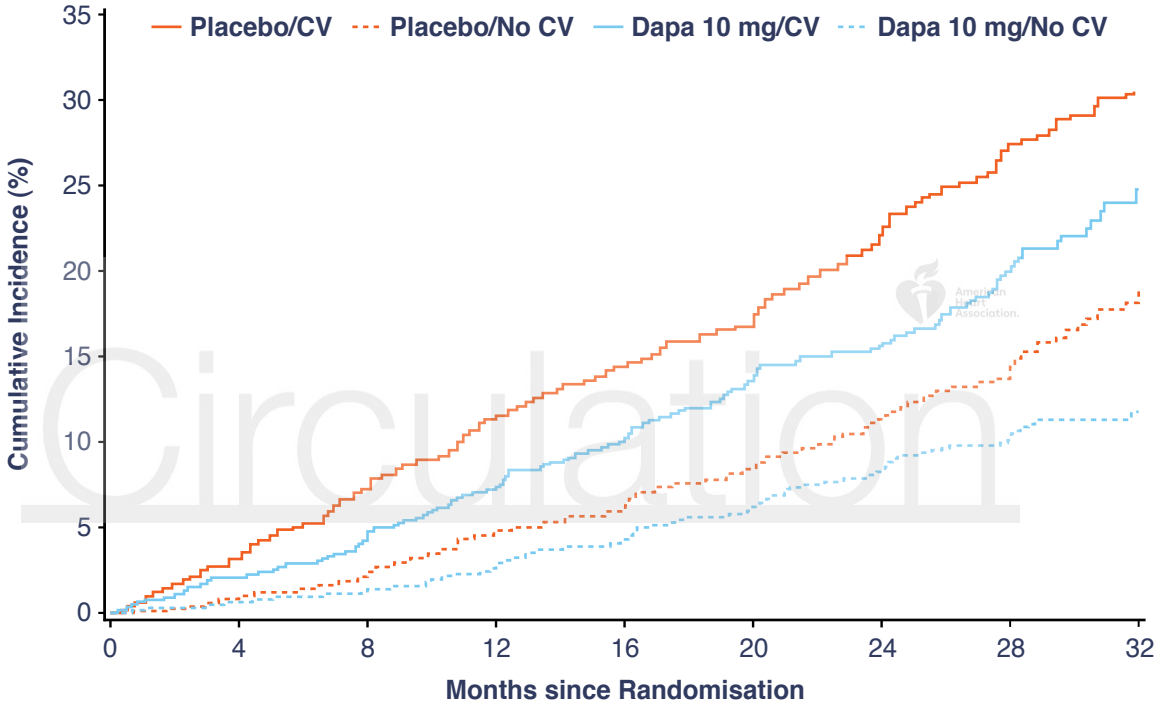
Death from any cause by CV history



No. at Risk

Dapa 10mg/CV	813	790	783	776	764	731	600	403	160
Dapa 10mg/No CV	1339	1249	1246	1241	1234	1194	931	625	238
Placebo/CV	797	770	759	745	734	702	566	386	137
Placebo/No CV	1355	1265	1259	1248	1238	1200	936	623	242

Posthoc CV/Renal endpoint by CV history



No. at Risk

Dapa 10mg/CV	813	771	747	715	687	627	493	305	114
Dapa 10mg/No CV	1339	1219	1194	1158	1127	1050	776	504	187
Placebo/CV	797	743	706	669	637	595	448	276	84
Placebo/No CV	1355	1231	1195	1151	1119	1041	772	490	188